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Case Report

Coexisting of cryptococcal pneumonia and rib osteomyelitis in an immunocompetent host: a case report and literature review

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Abstract: The presentation of synchronous cryptococcal osteomyelitis and fungal pneumonia in immunocompetent and previously healthy patients is really uncommon. Herein, a 61-year-old immunocompetent male patient with rib osteomyelitis and a solitary pulmonary nodule was presented. The patient was empirically diagnosed as malignancy on admission, because his PET-CT revealed osteolytic destruction of the rib. The pulmonary nodule did not demonstrate abnormal uptake of ^{18}F-FDG. Although CT-guided percutaneous biopsy of the rib showed nonspecific inflammation, surgery was decided to avoid delayed treatment. Subsequently, non-intubated uniportal thoracoscopic segmentectomy and partial resection of the diseased rib were performed successfully. Postoperative pathological staining of the specimen revealed his correct diagnosis as concurrent cryptococcal pneumonia and rib osteomyelitis. A sustained clinical response was achieved after antifungal therapy using oral fluconazole for 3 months. This report indicated that, fungal osteomyelitis should be kept in mind during the differential diagnosis of osteolytic rib lesions on radiological images, meanwhile, repeated pathological diagnosis via biopsy could be considered to avoid delayed treatment or unnecessary surgery. Timely diagnosis of rib osteomyelitis with sufficient antifungal therapy, with or without surgical intervention, may deliver complete eradication of the disease.

Keywords: Cryptococcosis, cryptococcal osteomyelitis, ground-glass nodule (GGN), coil labeling

Introduction

Cryptococcal infection is mainly due to the inhalation of infected spores or desiccated yeast cells, which is usually asymptomatic. It may cause numerous extrapulmonary infections. Nearly 10% of the disseminated cases involve bone tissues [1]. Manifestation of pulmonary cryptococcosis ranges from asymptomatic, isolated ground-glass nodule (GGN) to potentially fatal disseminated lesions. The presentation of fungal osteomyelitis in immunocompetent patients is rare [2]. Fungal infection of the rib maybe result from direct inoculation, contiguous infection from adjacent mycotic lesions or hematogenous seeding of the fungus. It might be associated with HIV infection, major surgery, antibiotic abuse, venous catheter insertion and immunosuppression.

The morphological and radiological characteristics of cryptococcal lesion is probably nonspecific during the differential diagnosis of infectious and neoplastic etiologies. Therefore, misdiagnosis and mistreatment of isolated fungal lesion is truly hard to avoid completely. Management of fungal osteomyelitis is sometimes challenging. To date, there is no clear consensus on the optimal therapeutic choice because of its rarity. Antifungal chemotherapy is the mainstay of treatment, and a limited surgery could be considered for resectable cases after the control of disseminated cryptococcosis. A correct diagnosis is essential to avoid delayed therapy and unnecessary aggressive surgery. Antifungal therapy combined with selective resection of the osteolytic lesion could be considered to achieve a complete eradication of the debilitating infection.

Herein a special case with synchronous cryptococcal pneumonia and isolated rib cryptococcal osteomyelitis was presented for discussion, followed by a brief review of the characteristics

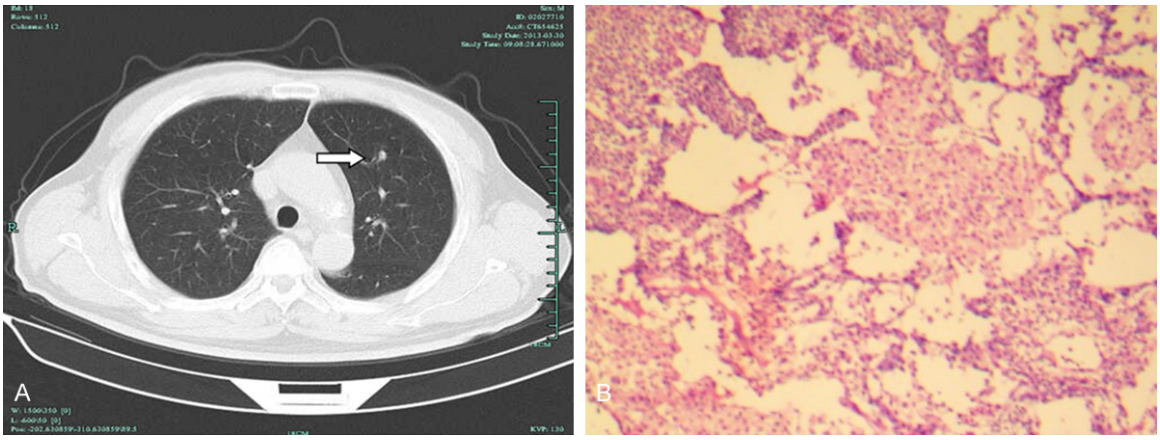

Figure 1. A. Chest CT of the patient on admission showed an isolated GGN in left upper lobe, measuring about 6 mm×3 mm in size (arrow); B. The pulmonary GGN was diagnosed as fungal pneumonia (H&E staining, ×200).

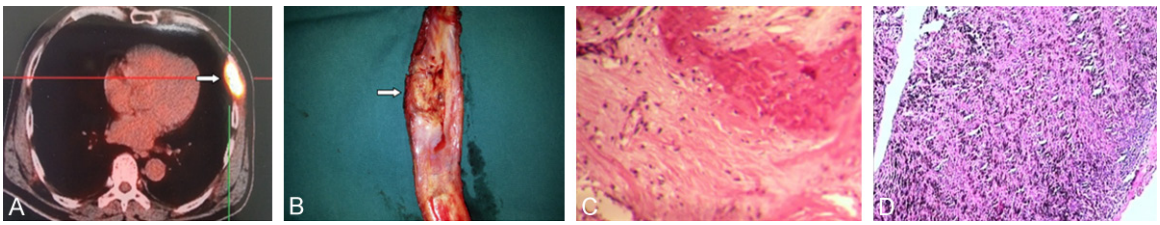

Figure 2. A. PET-CT showed an irregular mass in the left 6th rib about 35 mm×20 mm in size, with significantly abnormal uptake of the fluorodeoxyglucose (arrow); B. The resected rib showed bone destruction morphologically (arrow); C. The rib was diagnosed as granulomatous inflammation by intraoperative frozen section examination (H&E staining, ×200); D. Positive periodic acid-Schiff (PAS) staining of the rib demonstrated Cryptococcus organisms (×200).

and therapeutic regimen of cryptococcal osteomyelitis.

Case presentation

A 61-year-old male patient was admitted because of slight cough and moderate chest pain for one month, without fever, chills or significant loss of weight. The patient had suffered from type 2 diabetes mellitus for more than 5 years, without contact history with live birds or other poultry. Physical examination revealed an irregular, palpable protruded mass measuring 35 mm×20 mm in size, which was located in the left 6th rib along the anterior axillary line, with mild tenderness. Further tests were carried out step by step for differential diagnosis of benign lesion and malignancy.

Laboratory blood examinations showed that his CD4+ lymphocyte count, neutrophilic granulocyte count, erythrocyte sedimentation rate, human immunodeficiency virus (HIV) antibody, and the tumor markers such as carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), squamous cell carcinoma (SCC) and neuron specific enolase (NSE) were all in normal range. The cryptococcal antigens in serum and cerebrospinal fluid were negative. In addition, bronchoscopy and bronchoalveolar lavage failed to make a definite diagnosis.

Computed tomography (CT) showed an isolated GGN about 6 mm×3 mm in size, which was located in the anterior segment of the left upper lobe (**Figure 1A**). It demonstrated a standard uptake value max (SUVmax) of 1.9 on positron emission tomography-computed tomography (PET-CT). Besides, the CT revealed an synchronous irregular mass in the left 6th rib measuring 35 mm×20 mm in size, which demonstrated osteolytic behavior on PET-CT with a SUVmax of 19.2. It broke through the cortex of the rib and invaded into the adjacent parietal pleura (**Figure 2A**). Preoperative biopsy of the rib lesion revealed nonspecific inflammation without fungus or tuberculosis.

Table 1. Similar reports of cryptococcal rib osteomyelitis in immunocompetent patients

Year	Number of cases	Diagnosis method	Treatment	Prognosis
1953 [14]	1	Not available	Not available	Not available
1982 [15]	1	Pathology and culture	Not available	Not available
1990 [16]	1	Pathology	Not available	Not available
1998 [17]	1	Pathology	Resection and chemotherapy	Complete eradication
2005 [18]	1	Not available	Chemotherapy	Complete response
2005 [19]	1	Pathology	Resection and chemotherapy	Complete eradication
2010 [20]	1	Pathology	Not available	Not available
2010 [21]	1	Morphological investigation	Resection and chemotherapy	Complete eradication
2011 [22]	1	Culture	Chemotherapy	Complete response
2012 [23]	1	Pathology	Chemotherapy	Complete response
2015 [12]	1	Infectious etiology	Not available	Not available

Based on these findings, the patient was empirically diagnosed as lung cancer with osseous metastasis. To diminish the risk of delayed therapy, minimally invasive resection of the lesions was decided after multidisciplinary consultation. Informed consent was obtained from the patient before surgery. The pulmonary GGN was preoperatively located by CT-guided percutaneous coil labeling to ensure its complete resection. Then uniportal thoracoscopic segmentectomy and excision of the diseased rib were carried out. The segmentectomy was performed using artificial pneumothorax without endotracheal intubation as previously reported [3], utilizing a laryngeal mask for inhalation of oxygen.

The excised rib was morphologically identified as granuloma (**Figure 2B**). It was initially diagnosed as granulomatous inflammation by intraoperative frozen section examination (**Figure 2C**). The pulmonary GGN was pathologically diagnosed as fungal pneumonia (**Figure 1B**). The rib mass was turned out to be osteolytic cryptococcosis with positive staining by periodic acid methenamine silver (PAM) and periodic acid-Schiff (PAS), which revealed numerous Cryptococcus organisms (**Figure 2D**). Based on these findings, his diagnosis was corrected as concurrent cryptococcal pneumonia and rib osteomyelitis. However, a culture from the involved rib failed to yield Cryptococcus neoformans.

His postoperative recovery was mainly uneventful, and he was discharged 5 days after the surgery. The patient was treated with oral fluconazole of 200 mg daily for three months after the operation. Thereafter, he demonstrated satisfactory quality of life without recurrence of the fungal infection during the follow up by smartphone for 3 years up to now.

Discussion

Cryptococcosis is a global invasive mycosis associated with significant morbidity and mortality in both immunocompromised and apparently immunocompetent hosts. Besides, diabetes mellitus is associated with the occurrence of cryptococcosis and cryptococcal meningitis in HIV-uninfected patients, as well as the 1-year and overall mortality of these patients [4]. Inhalation of Cryptococcus into the respiratory system is the main route of infection, and severe hematogenous dissemination can result in potentially fatal meningoencephalitis [5]. Cryptococcus neoformans could form titan cells which can reach up to 100 μm in diameter during pulmonary infection, which might result in misdiagnosis as pulmonary tumors empirically [6]. Moreover, vascular malformation might be a pathological predisposing factor for local pulmonary cryptococcosis [7].

Clinical manifestation of pulmonary cryptococcosis is mainly nonspecific, and the current diagnostic tests lack sensitivity and specificity, therefore, the differential diagnosis of cryptococcosis, neoplastic lesions, tuberculosis and other infections is sometimes challenging. The initiation of treatment is often based solely on clinical suspicion [8], consequently, misdiagnosis and overtreatment is hard to prevent completely. Cryptococcal osteomyelitis should be suspected in immunocompetent patients with osteolytic lesions on radiological images. Pulmonary cryptococcosis mimics primary or met-

astatic lung cancer on PET-CT because of its active metabolism, therefore, pathological confirmation is necessary for any suspicious pulmonary nodules with an SUV score higher than 2.5 to avoid overdiagnosis or overstaging [9]. Moreover, fungus culture and special staining such as PAS and PAM are useful for timely diagnosis of cryptococcosis.

In addition to surgery, the treatment for cryptococcosis is largely limited to amphotericin B (and its liposomal derivatives), 5-fluorocytosine (5-FC) and fluconazole [10]. The current standard therapy is amphotericin B combined with 5-flucytosine, which is always correlated with significant systemic toxicity [11]. The presenting patient is treated successfully with limited resection of the involved lung and rib, followed by antifungal chemotherapy. However, due to the rarity of cryptococcal osteomyelitis, there are no specific recommendations regarding the optimal treatment [12]. A timely and aggressive intervention may be reasonable for selected patients with cryptococcal osteomyelitis, which could be considered to diminish severe complications such as pathological rib fracture.

On the other hand, as compared with intubated procedure and one-lung ventilation, it is reported that non-intubated, intravenous anesthesia with spontaneous ventilation demonstrates certain advantages. Meanwhile, patients who underwent segmentectomy without tracheal intubation could gain a prompt recovery with comparable short-term outcomes [13], which is in accordance with the principles of precision medicine as well as fast track in thoracic surgery.

Furthermore, similar reports involving cryptococcal rib osteomyelitis in immunocompetent patients are indicated in **Table 1** [12, 14-23], with the aim to enhance the identification, diagnosis and therapy of fungal rib osteomyelitis. Briefly speaking, for patients admitted for pathological rib fraction, palpable mass on the ribs or osteolytic lesions in CT images, localized mycological infection should be considered during its differential diagnosis between inflammation and tumor. The diagnosis methods include pathological staining and culture of the specimen for fungus via fine needle biopsy or limited resection of the involved ribs. In addition, oral or intravenous antifungal chemotherapy with or without surgical debridement is still the major treatment for these patients, always followed by satisfactory prognosis. It is noteworthy that the rare possibility of fungal osteomyelitis in immunocompetent patients should not be ignored, in addition to the diabetic, immunosuppressive and elderly patients.

In summary, this presenting case indicates the feasibility and safety of non-intubated segmentectomy after coil labeling. Surgery combined with antifungal chemotherapy might be a reasonable choice for isolated cryptococcosis. However, high-quality studies regarding awake thoracic surgery are still needed.

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Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. This study was approved by the institutional review board of Shaoxing People's Hospital.

Disclosure of conflict of interest

None.

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